

# Physiological versus standard sex steroid replacement in young women with premature ovarian failure

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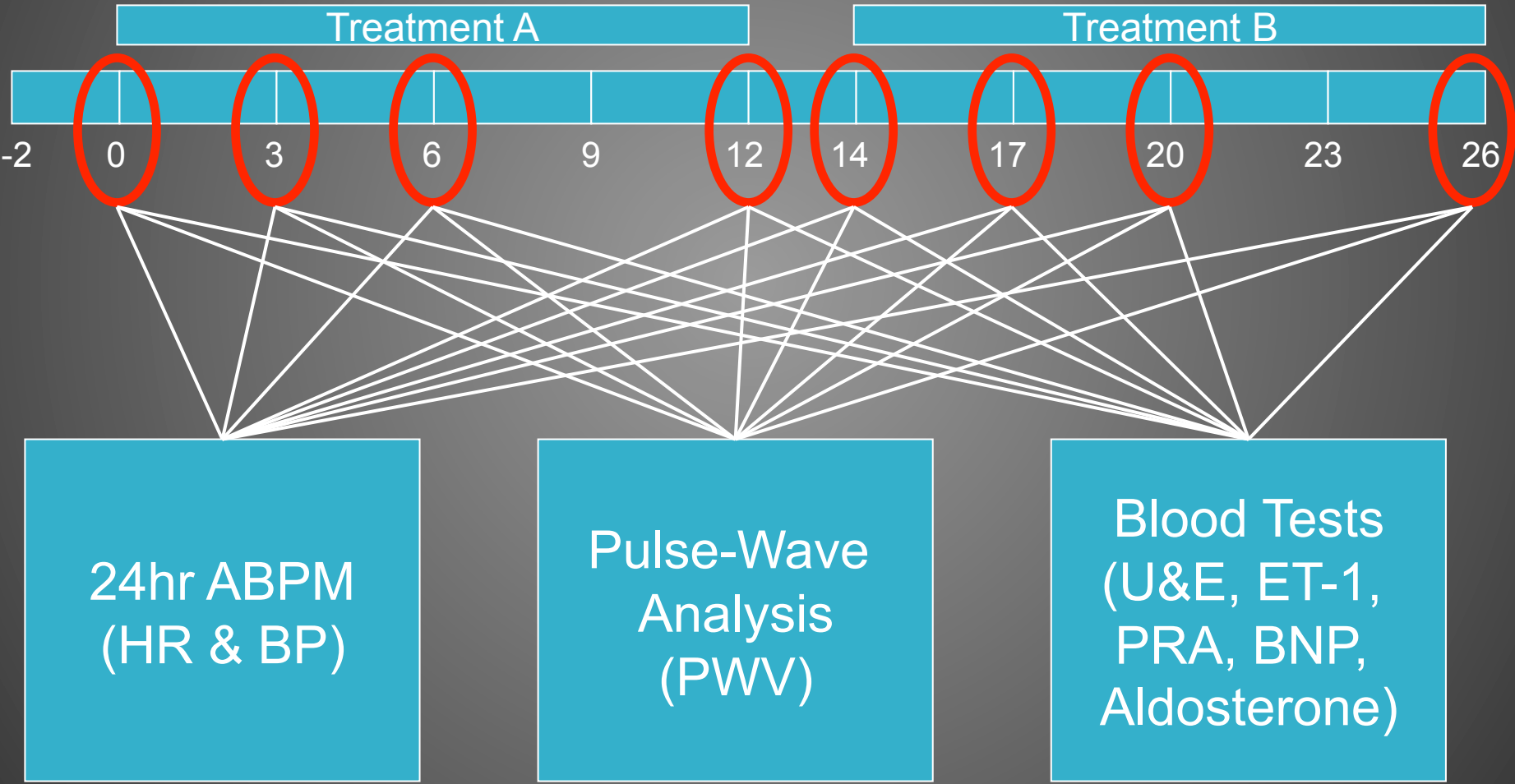
# Physiological versus standard sex steroid replacement in young women with premature ovarian failure

- Eligibility
- Documented premature ovarian failure <40 yrs.
- Aim:
- To establish whether we can improve skeletal, cardiovascular and uterine health with a physiological regimen of SSR in young women with premature ovarian failure due to different causes.

# Sex steroid replacement

- Physiological
- transdermal Oestradiol, 100 $\mu$ g/24h week 1, 150  $\mu$ g/24h weeks 2-4; vaginal progesterone, 200 mg/12 hourly weeks 3-4)
- Standard
- Loestrin 30: (30  $\mu$ g/24h ethinyloestradiol + 1.5mg/24h norethisterone acetate weeks 1-3, week 4 tablet-free)

# Study Design



24hr ABPM  
(HR & BP)

Pulse-Wave  
Analysis  
(PWV)

Blood Tests  
(U&E, ET-1,  
PRA, BNP,  
Aldosterone)

## Baseline characteristics of subjects who completed the study compared with subjects who subsequently withdrew from the study

Characteristic	Completed	Withdrew
	n = 18	n = 17
Aetiology of ovarian failure: Turner's / Childhood cancer / Adult-acquired	7 / 4 / 7	2 / 4 / 11
Age, years	27 (23 – 30)	31 <sup>a</sup> (28 – 34)
Height, cm	160 (156 – 164)	162 (157 – 168)
Weight, kg	71.4 (62.3 – 80.4)	72.3 (62.7 – 81.9)
BMI, kg/m <sup>2</sup>	27.7 (24.8 – 30.7)	27.1 (24.4 – 29.9)
Treatment order: pSSR-sHRT / sHRT-pSSR	6 / 12	11 / 6

## Baseline anthropometry and BMD according to aetiology of ovarian failure

	<u>Turner</u>	<u>Childhood cancer</u>	<u>Adult-acquired</u>
<u>N</u>	<u>9</u>	<u>8</u>	<u>18</u>
<u>Age (y)</u>	<u>22</u> (20 – 24)	<u>31</u> (27 – 36)	<u>31</u> (28 – 34)
<u>Height (cm)</u>	<u>152</u> (148 – 157)	<u>162</u> (155 – 169)	<u>165</u> (161 – 169)
<u>Weight (kg)</u>	<u>63.4</u> (49.9 – 76.8)	<u>64.4</u> (53.4 – 75.4)	<u>79.3</u> (70.4 – 88.2)
<u>Lumbar spine aBMD z score</u>	-1.13 (-1.90 to -0.37)	-0.46 (-1.19 to +0.26)	-0.16 (-0.77 to +0.45)
<u>Femoral neck aBMD z score</u>	-0.84 (-1.81 to +0.12)	-0.46 (-1.07 to +0.14)	+0.16 (-0.48 to +0.80)
<u>Total hip aBMD z score</u>	-0.62 (-1.52 to +0.27)	-0.38 (-1.16 to +0.41)	+0.21 (-0.32 to +0.75)
<u>Lumbar spine trabecular vBMD z score</u>	<u>-0.29</u> (-0.97 to +0.39)	<u>+0.23</u> (-0.76 to +1.22)	<u>+0.10</u> (-0.31 to +0.51)

Data are expressed as mean (95% CI mean).

## Hormone levels after first wash-out and during pSSR and sHRT

Hormone	After first washout	pSSR	sHRT
LH (U/L)	38.9 (30.3 – 47.5)	13.5 (7.6 – 19.4)	8.0 (5.0 – 11.1)
FSH (U/L)	85.8 (67.8 – 103.8)	21.0 (13.8 – 28.2)	17.3 (9.9 – 24.7)
Oestradiol (pmol/L)	66 (51 – 81)	406 (280 – 532)	66 (50 – 83)
Progesterone (nmol/L)	4.9 (4.2 – 5.6)	5.7 (5.0 – 6.3)	4.8 (4.2 – 5.3)

## Changes in BMD in response to physiological SSR and standard HRT

BMD measurement	pSSR	sHRT
Lumbar spine aBMD z-score	+0.17 <sup>a</sup> (+0.07 to +0.27)	+0.07 (-0.03 to +0.18)
Lumbar spine trabecular vBMD z-score	+0.02 (-0.19 to +0.22)	+0.04 (-0.10 to +0.18)
Femoral neck BMD z-score	+0.12 (-0.05 to +0.29)	+0.11 (-0.04 to +0.25)
Total Hip BMD z-score	-0.04 (-0.16 to +0.08)	0.03 (-0.08 to +0.13)

Data are expressed as mean (95% CI mean)

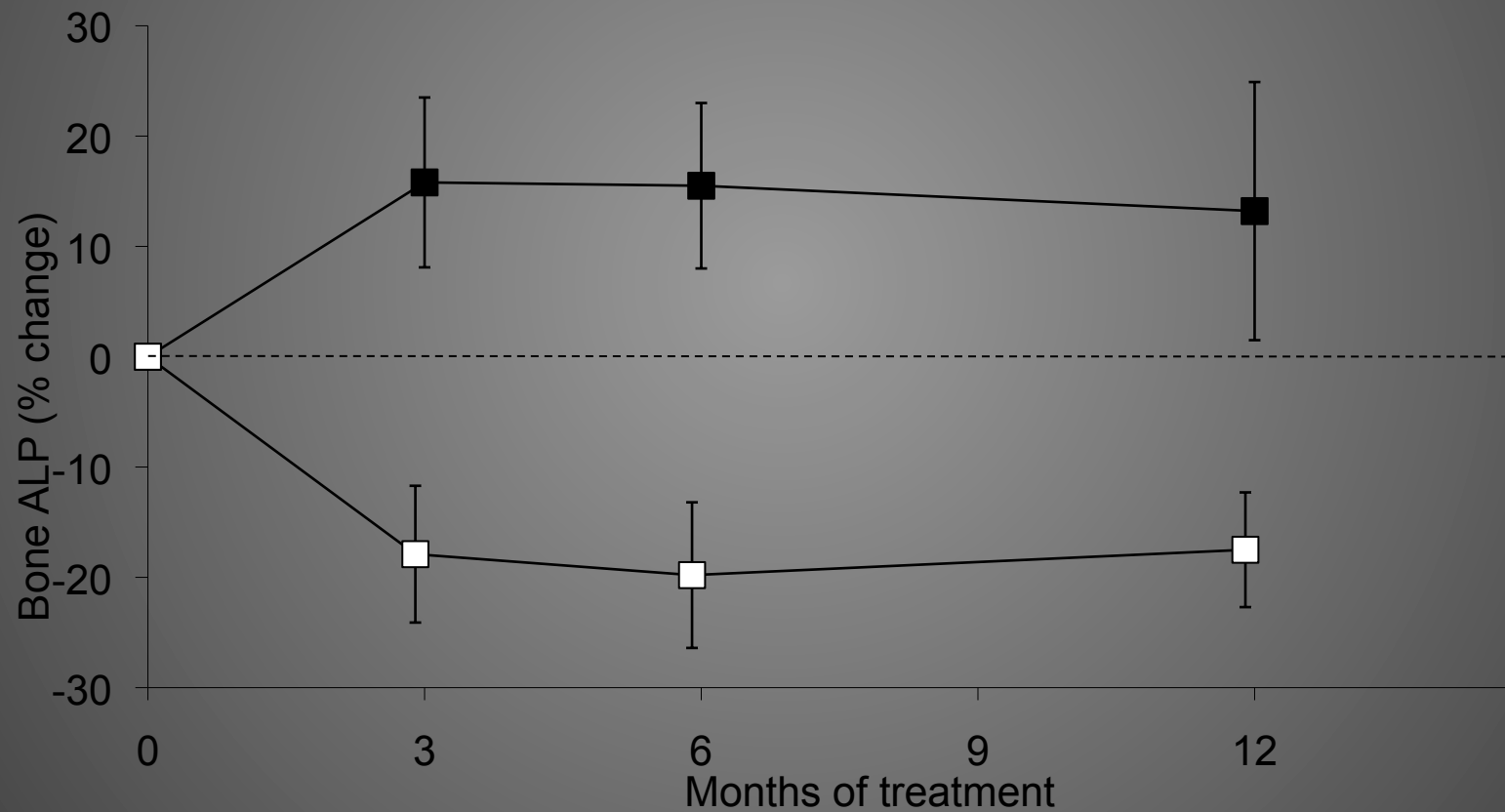
<sup>a</sup> P <0.01 versus baseline aBMD z score



Percentage changes in bone markers compared with post wash-out baseline in response to pSSR (solid squares) and - HRT (open squares).

Bone ALP

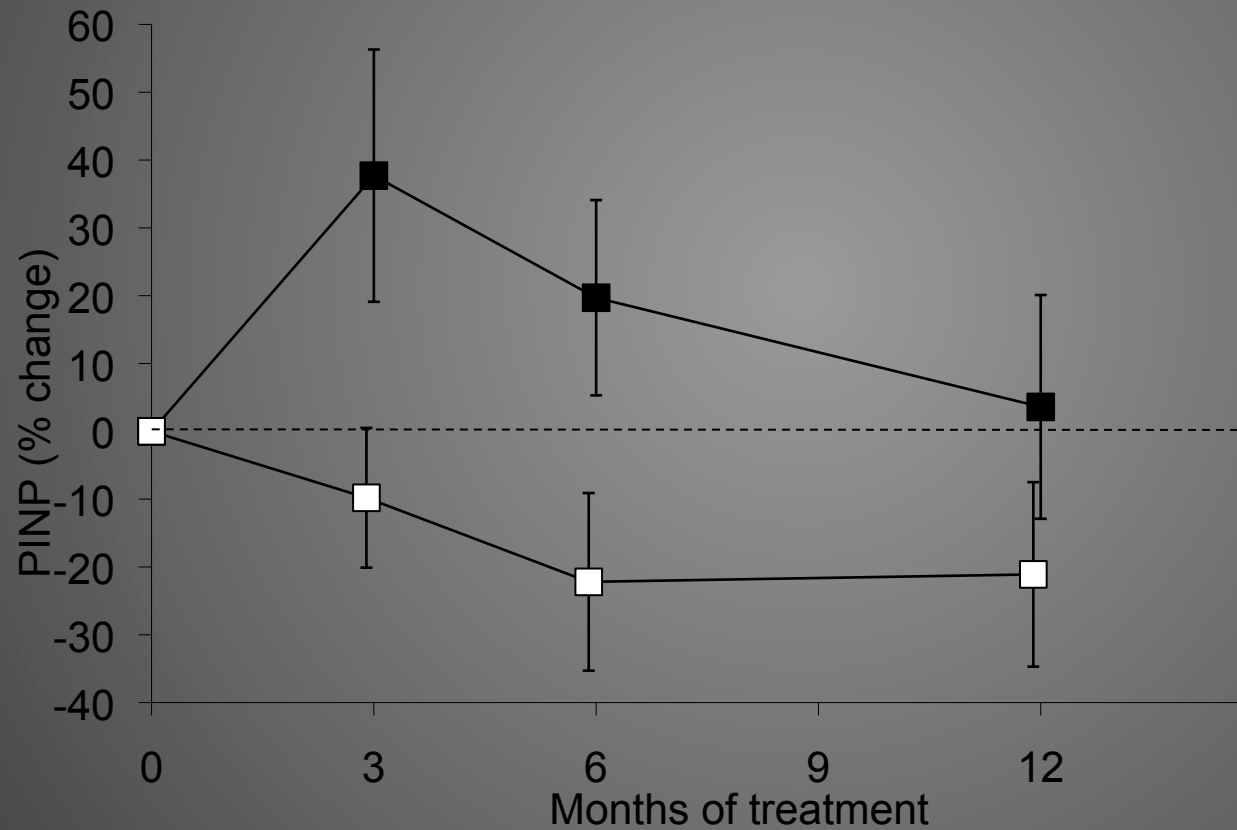
Data are expressed as mean (95% CI).



Percentage changes in bone markers compared with post wash-out baseline in response to pSSR (solid squares) and s HRT (open squares).

PINP

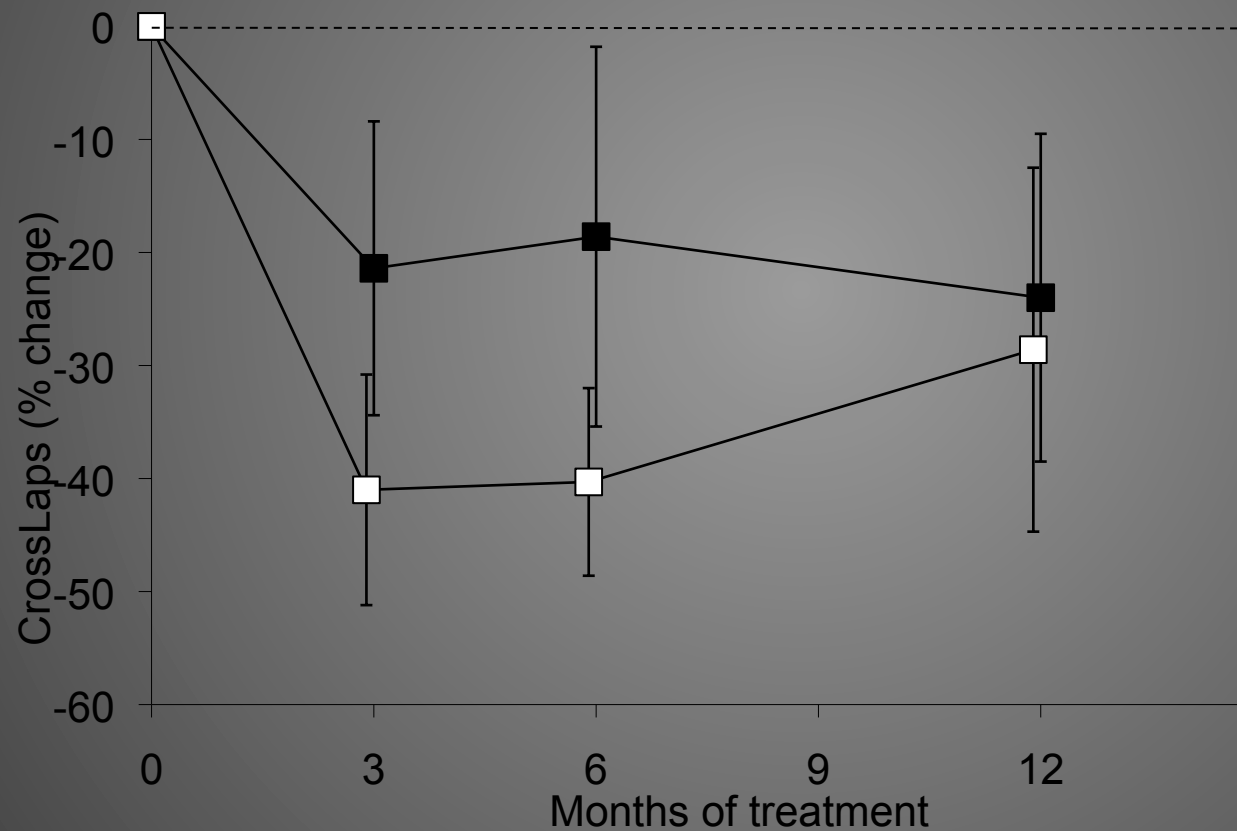
Data are expressed as mean (95% CI).



Percentage changes in bone markers compared with post wash-out baseline in response to pSSR (solid squares) and s HRT (open squares).

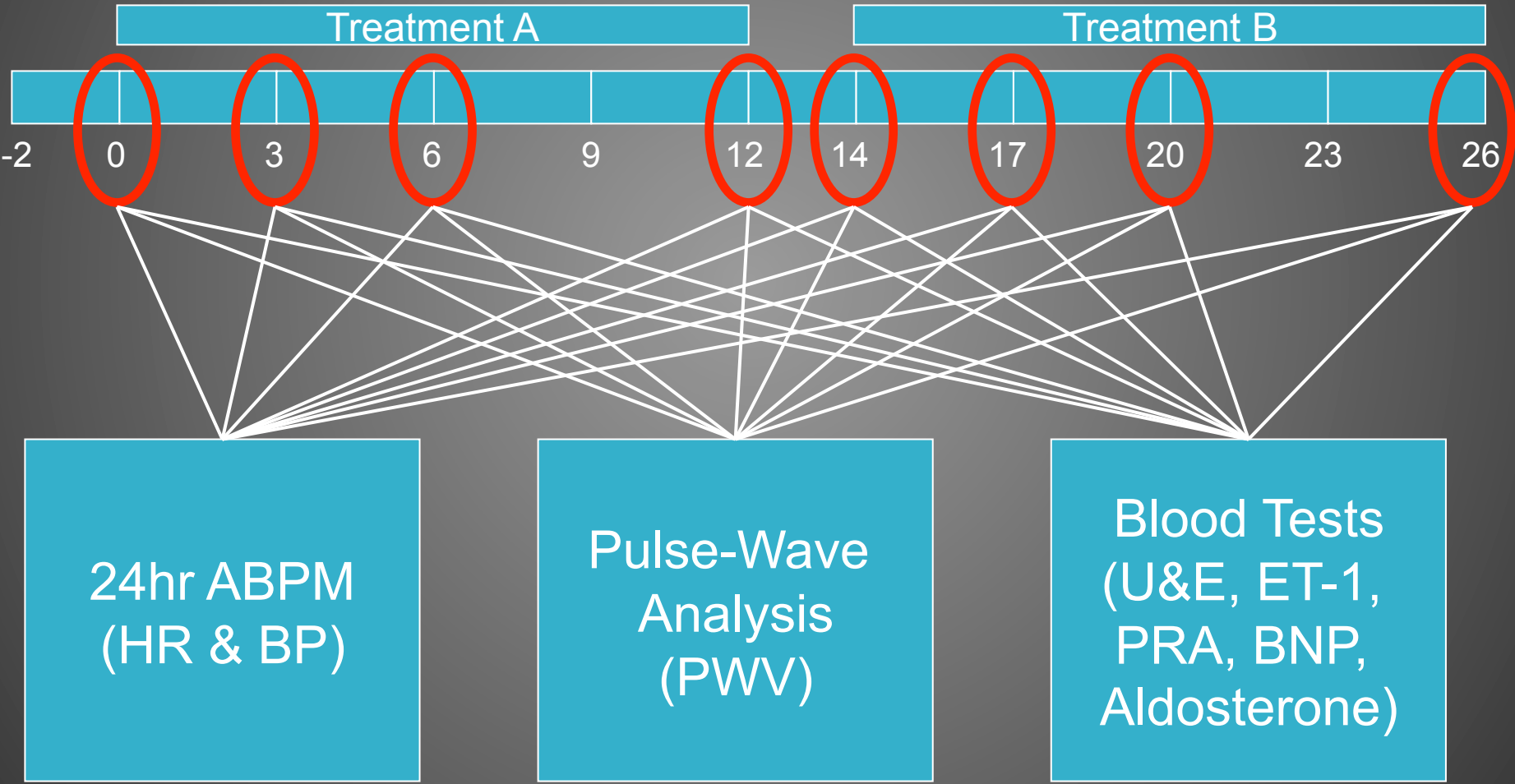
CrossLaps.

Data are expressed as mean (95% CI).



# Haemodynamic Changes with Hormone Replacement

# Study Design

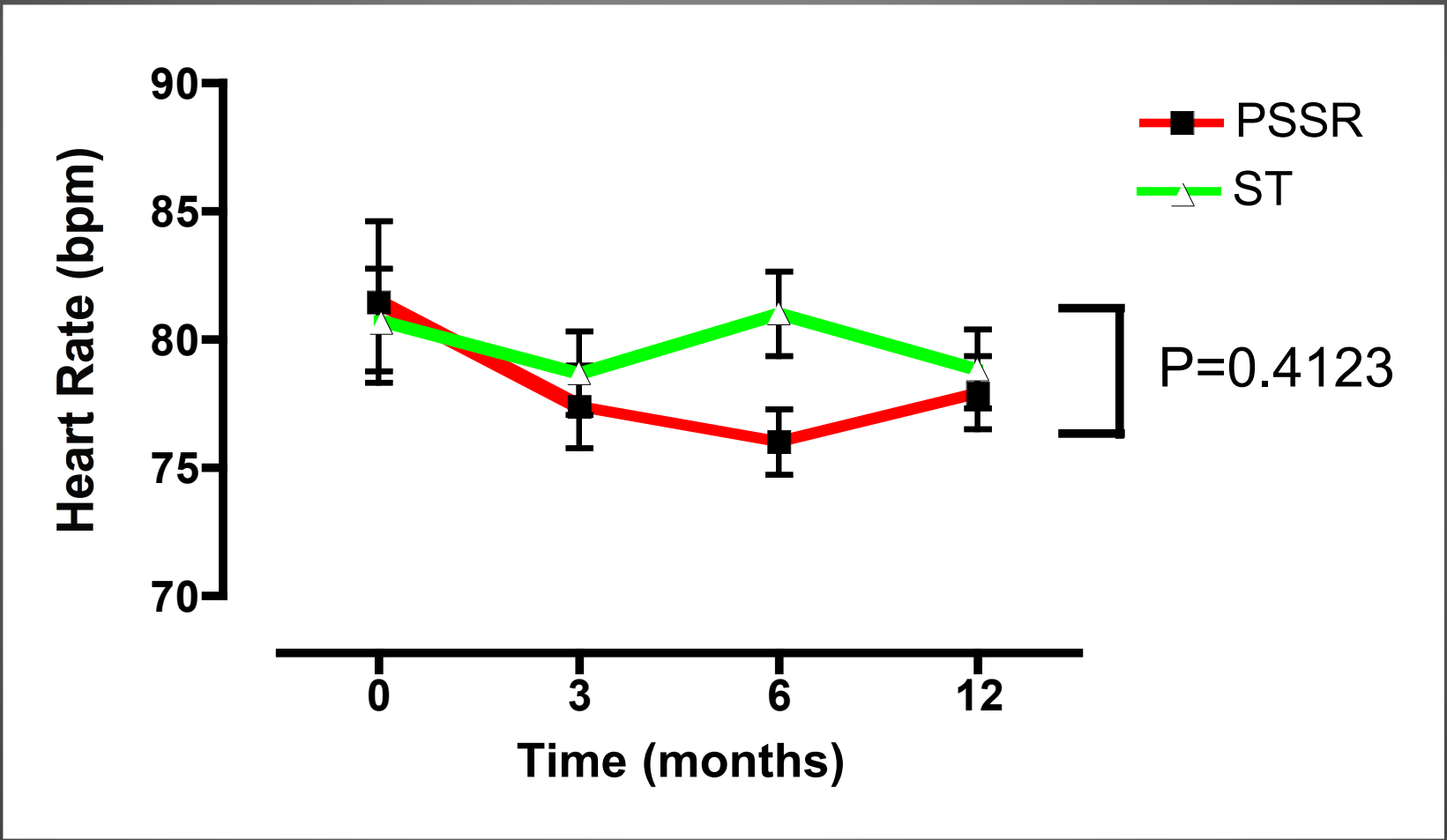


24hr ABPM  
(HR & BP)

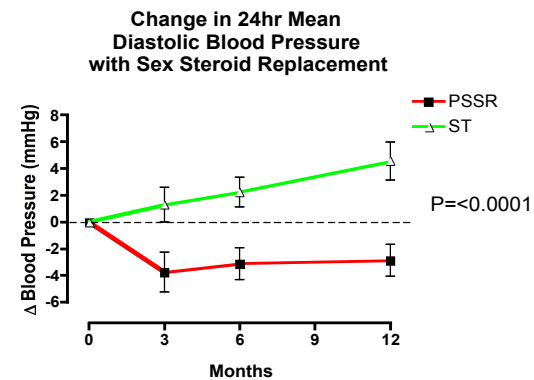
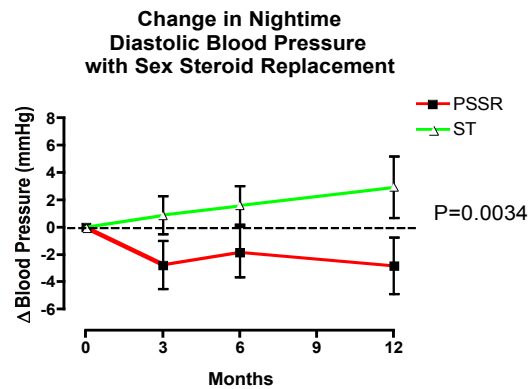
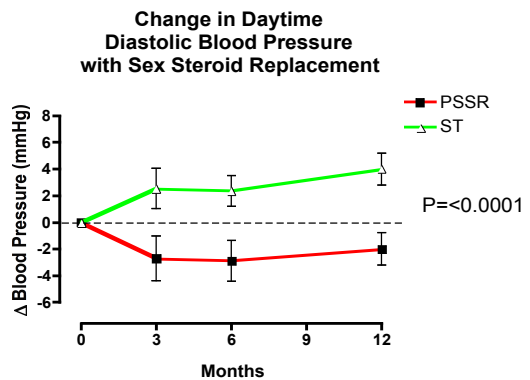
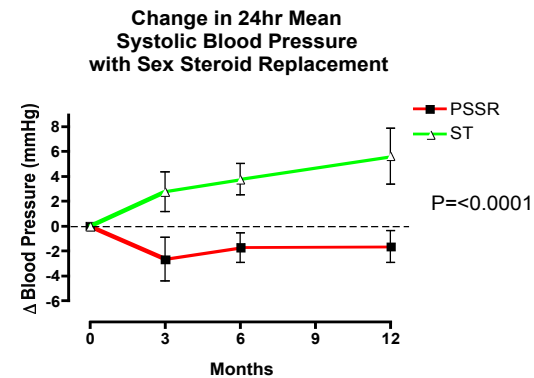
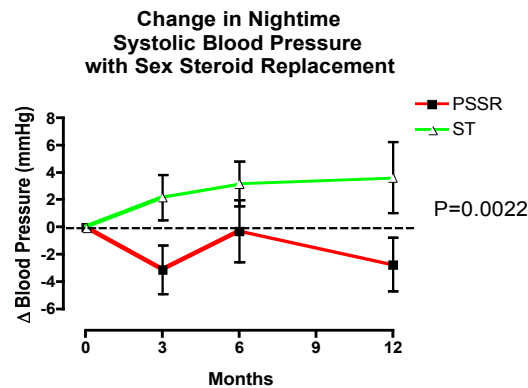
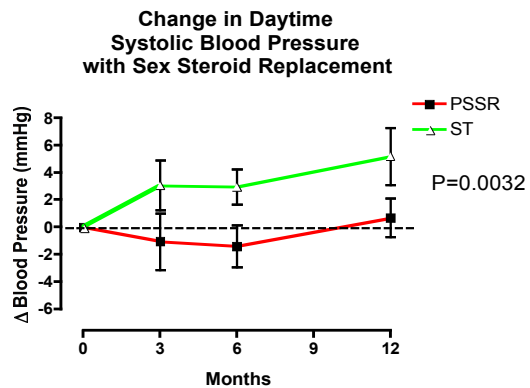
Pulse-Wave  
Analysis  
(PWV)

Blood Tests  
(U&E, ET-1,  
PRA, BNP,  
Aldosterone)

# Heart Rate Changes

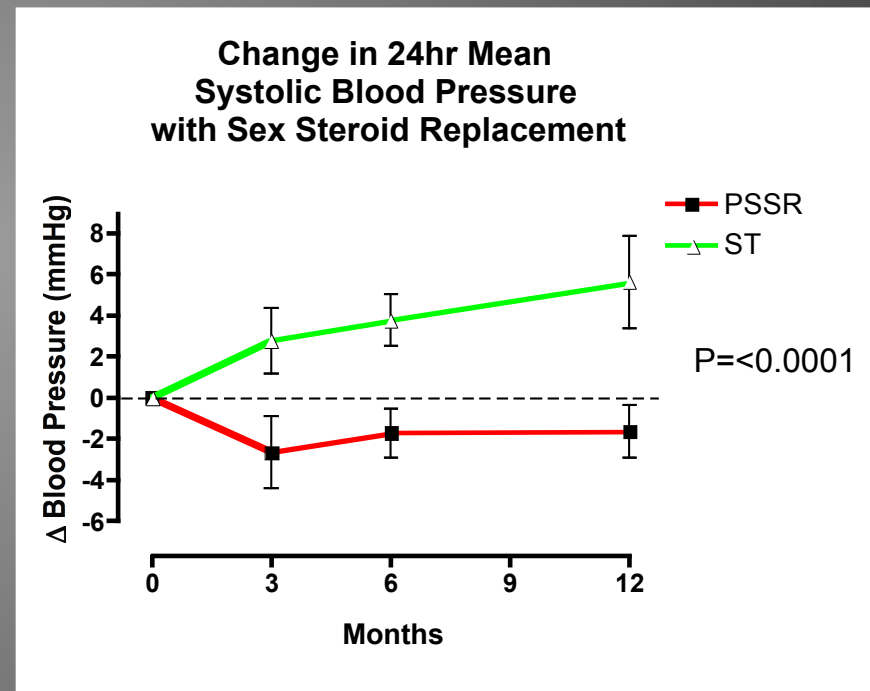


# Blood Pressure Changes



# Blood Pressure Changes

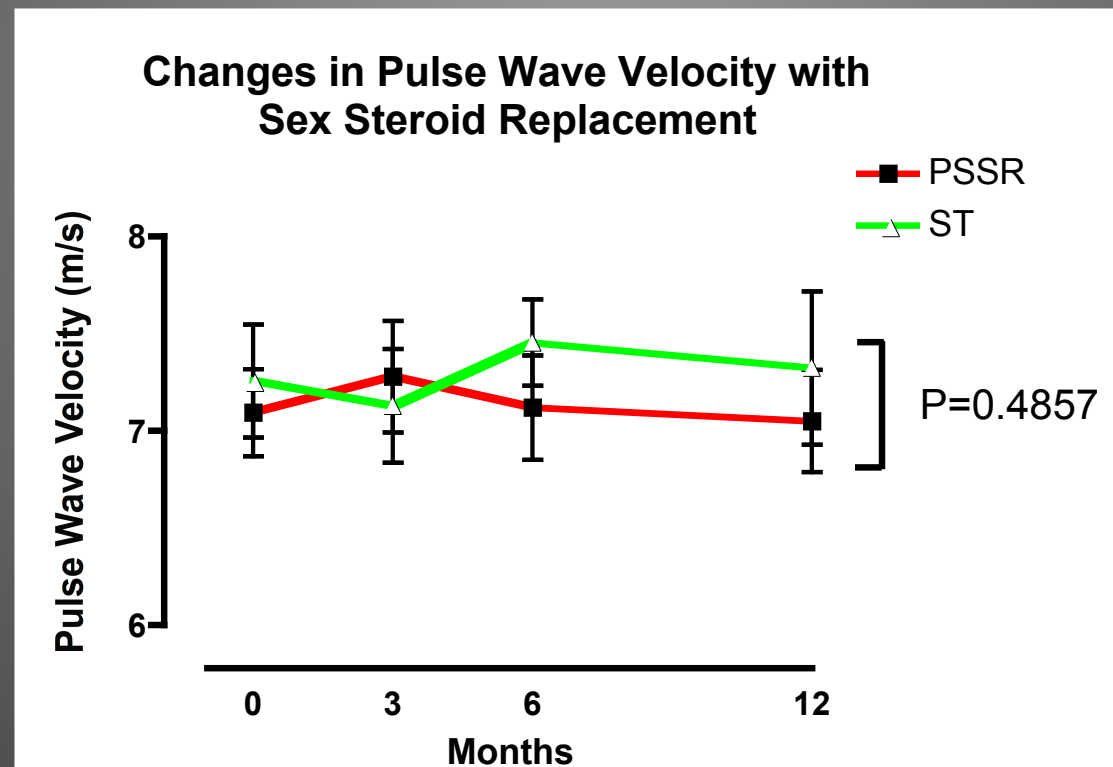
- 1.6mmHg reduction with PSSR (SBP)
- 5.6mmHg increase with ST (SBP)
- OVERALL 7.2mmHg SBP BENEFIT WITH PSSR





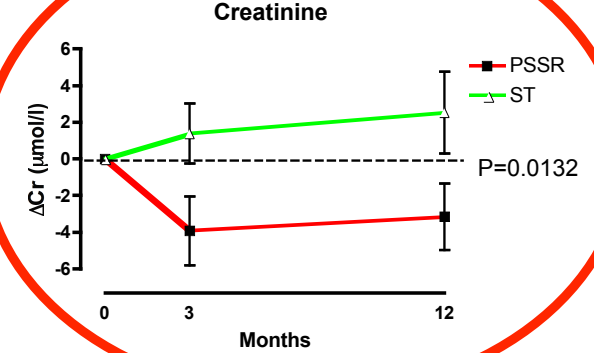
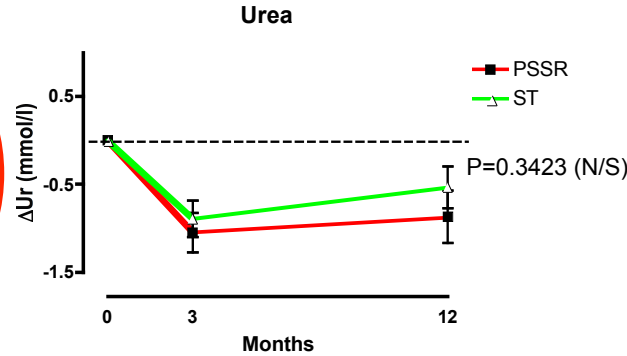
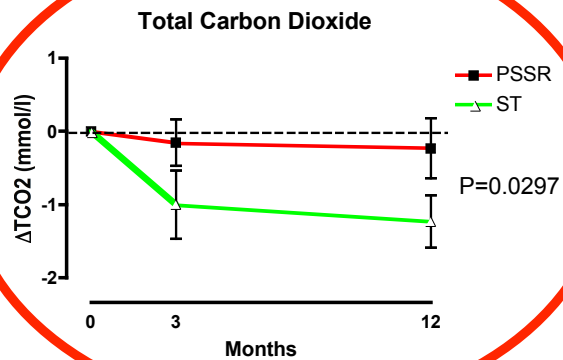
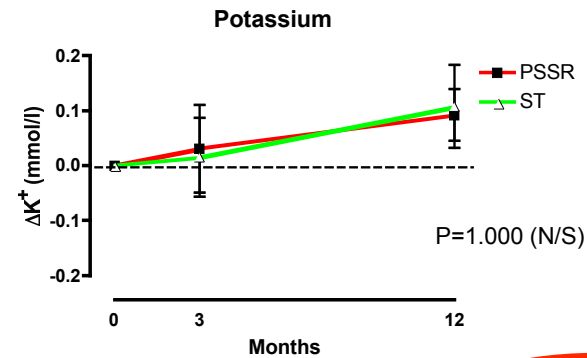
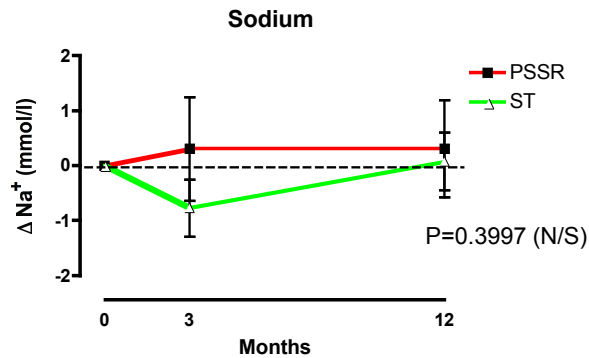
# Mechanism of Blood Pressure Changes?

- Does not appear to be related to changes in central arterial stiffness...



# Mechanism of Blood Pressure Changes?

- Effect on renin-angiotensin system?



# Mechanism of Blood Pressure Changes?

- Effect on renin-angiotensin system?
- Other neurohormonal circulating factor?

Results of biochemical assay are still awaited....

Blood Tests  
(U&E, ET-1,  
PRA, BNP,  
Aldosterone)

# Acknowledgements

- *Crofton PM,*
- *Evans N,*
- *Bath L E,*
- *Warner P,*
- *Critchley HOD,*
- *Kelnar CJH,*
- *Langrish J,*
- *Newby D,*
- *Webb D*

# Proposal

- Premature ovarian failure
- Randomised five centre study
- Physiological versus Standard
- Two years
- No wash out
  - Skeletal health (BMD)
  - Cardiovascular Health
  - Uterine Health

Evaluation of Sex sTeROid  
replacement reGimens in  
prematurE ovariaN failure

The 5LEGS ESTROGEN  
trial